[*Reprinted from the* PROCEEDINGS OF THE ROYAL SOCIETY OF MEDICINE, *1928, Vol. XXI (Section of Tropical Diseases and Parasitology, pp. 1—15).*]

IMPERIAL BUREAU OF MYCOLOGY

NOTES ON BLASTOMYCOSIS: ITS ÆTIOLOGY AND CLINICAL VARIETIES.

By ALDO CASTELLANI, C.M.G., M.D., F.R.C.P.

(From the Ross Institute, London, and the Tulane University of New Orleans, U.S.A.)

THE term blastomycosis cutis, *sensu lato*, is used to denote any pathological condition of the skin due to the so-called "yeast-like fungi," or "budding fungi."

Yeast-like Fungi.—The term "yeast-like fungi" is unscientific, but useful in practice. Yeast-like fungi are fungi which in the lesions appear as oval or roundish cells, some of them budding, with no mycelium. Morphologically, in the lesions two principal types of yeast-like fungi may be distinguished: (*a*) the *blastomycetoid* type, (*b*) the *saccharomycetic*, or *cryptococcoid* type.

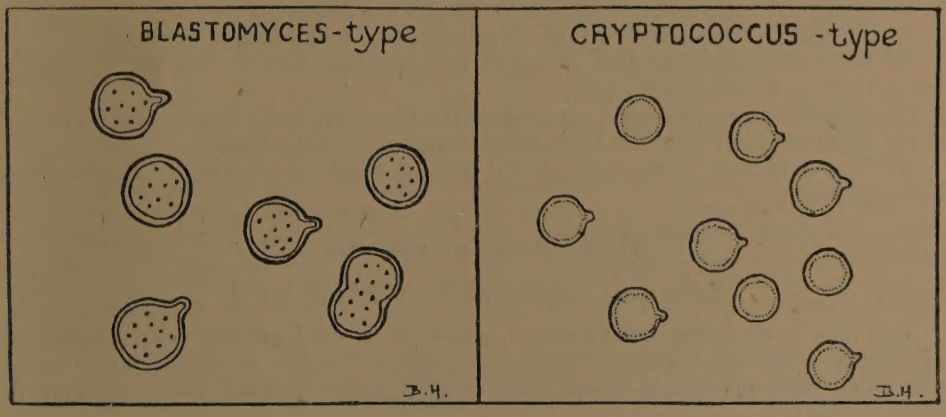

FIG. 1.—Fungi in the lesions.

The characters of the blastomycetoid type are the following: Cells larger, double contour very well marked, granules in the protoplasm very evident and of comparatively large dimensions. The characters of the saccharomycetic, or cryptococcoid type, are the following: Cells generally smaller, double contour absent or much less marked, protoplasmatic granules not so evident and usually much finer.

These fungi (of both types) belong to widely different botanical groups; when cultivated, some of them show the same morphological characters as in the lesions, viz., oval or roundish budding cells, with no mycelium, but quite a number of them show presence of mycelium, and some, in fact, mycelium only.

The late Dr. Chalmers and myself have given a botanical classification of these organisms in the third edition of our "Manual of Tropical Medicine." Some of them are ascomycetes, others are fungi imperfecti; the principal families to which they belong are the following:—

(*a*) In cultures, budding cells, and in addition asci and ascospores present, no mycelium—Family Saccharomycetaceæ, Rees, 1870.

(*b*) Same as (*a*), but mycelium present—Family Endomycetaceæ, Rees.

(*c*) In cultures, budding cells (blastospores) present, no asci and no mycelium—Family Cryptococcaceæ, Kützing, 1833.

(*d*) Same as (*c*), but mycelium present—Family Oosporaceæ, Saccardo.

Each family contains a number of genera, a brief description of which may be found in Castellani and Chalmers' "Manual of Tropical Medicine" (see also this paper, p. 7-11).

For the purpose of the clinician and clinical pathologist an elaborate botanical classification is not necessary, and some time ago I suggested the following simple scheme.

CLASSIFICATION OF YEAST-LIKE FUNGI.

"Yeast-like fungi." (In the lesions budding cells only, no mycelium.)
- Hanging-drop cultures
  - Free budding cells present
    - I. Mycelium absent, ascospores present—*Saccharomyces sensu lato.*
    - II. Mycelium absent, ascospores present—*Cryptococcus sensu lato.*
    - III. Mycelium present, ascospores present—*Endomyces sensu lato.*
    - IV. Mycelium present, ascospores absent—*Monilia sensu lato.*
  - Free budding cells absent
    - V. Mycelium present in large amount, ascospores absent—*Blastomycoides.*

THE PRINCIPAL CLINICAL TYPES OF BLASTOMYCOSIS CUTIS.

The principal types of blastomycosis cutis are the following:—

(1) Blastomycosis verrucosa (syn. Blastomycosis, Gilchrist type).

(2) Blastomycosis ulcerativa profunda seu mutilans (Blastomycosis, Wernicke-Ophül type or Coccidioides type).

(3) Blastomycosis purulenta profunda (syn. Blastomycosis, Busse type).

(4) Blastomycosis glutealis (syn. Blastomycosis, Kartulis type).

(5) Blastomycosis furunculosa (syn. Blastomycosis furunculosa, Furunculosis blastomycetica.

(1) *Blastomycosis verrucosa.*

(Synonym: Blastomycosis, Gilchrist type.)

This type is characterized by raised, roundish or oval patches with a verrucoid papillomatous or frambœsiform surface, somewhat similar to tuberculosis verrucosa cutis, and in certain cases frambœsia. The following subtypes may be differentiated:—

(1) Affecting usually the skin only, but may, in addition, in a later stage affect the mucosæ and internal organs; found all over the world, but principally in tropical and sub-tropical countries—Gilchrist type, *sensu stricto.*

(2) Affecting solely or principally the oral or nasal mucosa; this type is especially common in South America. It is known also as South American oral blastomycosis or blastomycosis Lutz-Splendore type, and a description of it may be found in Castellani and Chalmers' "Manual of Tropical Medicine," third addition, p. 2084.

(3) Affecting the tongue, causing at times an enormous increase in the size of this organ (macroglossia blastomycetica).

(4) Affecting first the skin and later the internal organs, with symptoms of general infection and pyæmia (systemic blastomycosis).

Illustrative Cases.

I will briefly quote nine cases among those I have had the opportunity of investigating. Four cases have been observed in England, but three of them contracted the affection abroad; five cases were observed in Louisiana (U.S.A.).

Case I.—Mr. M., while in Egypt during the Great War, noticed a papule near the left angle of the mouth, which later became moist and was covered by a small yellow crust. Other papules appeared and a patch formed. He reported to the medical officer who suggested syphilis. The Wassermann reaction was negative; he had, however, a course of neosalvarsan without any benefit. During this treatment the condition spread to the mucosa of the lips and later to the tongue. After leaving the Army he consulted various medical men, some of whom suspected syphilis, others a tuberculide. Finally, in 1920, he went to see Sir James Cantlie, who kindly referred him to me. I suspected blastomycosis, and succeeded in growing a fungus, which recent investigation has shown to be very similar to *Blastomyces tulanensis*. After several relapses he apparently recovered completely after a treatment of potassium iodide in large doses, and vaccine.

Case II (blastomycosis of the nose).—Mr. T., of Bradford, consulted me in January, 1921; he had a rather large papillomatous mass on the left ala of the nose, with severe loss of substance. The condition had started during the war while the patient was in the Balkans, and had been considered a syphilide or a tuberculide. He had been treated with salvarsan, mercurial preparations and X-rays. I grew a fungus with characters somewhat similar to blastomycosis dermatitidis; in addition, a monilia-like fungus was grown with all the biochemical characters of *Monilia metalondinensis*. The condition yielded to potassium iodide in massive doses, but it took more than a year for a complete cure to be achieved.

Case III (mild type of oral blastomycosis).—Master N. four years ago showed white patches on the tonsils and oral mucosa, apparently very similar to patches of thrush. Later several flattened nodules developed on the mucosa of the lower lip with a papillomatous surface. For these patches various diagnoses were suggested and various treatments were carried out without any benefit. He consulted me two years ago. The surface of one of the patches was scraped and from the deep parts of the lesion a fungus was found with the characters of a monilia, biochemically similar to *Monilia metalondinensis*.

The characters of the fungus are briefly the following:—In the lesions only roundish budding cells are seen; in cultures a slight amount of mycelium is present. Milk not clotted. Gas produced in glucose, levulose, maltose and galactose.

Case IV—(blastomycosis of the tongue) *Macroglossia blastomycetica*.—In Ceylon, during the period 1903-1915, I observed three cases of a peculiar type of macroglossia of blastomycotic origin. Four years ago an interesting case of the same type was kindly sent to me by my friend, Dr. Broughton Alcock. The tongue was enormously enlarged and occasionally painful; the patient felt discomfort in eating and difficulty in speaking; he could not whistle; the surface of the tongue was somewhat roughened in places, but no very typical verrucoid patches were present.

Deep scrapings were made from the tongue, after drying and painting with tincture of iodine, and cultures were made. A fungus was grown, which I at first placed in the genus Cryptococcus, and later in the genus Monilia: *Monilia macroglossiae*. (For description of the fungus see page 7.) A prolonged treatment with potassium iodide in very large doses and fungus vaccine induced an apparent cure.

Case V.—Mr. N., a white workman in New Orleans, two years ago, developed verrucose patches on the hands and forearms and on the face. A fungus was grown with the characters of *Blastomycoides dermatitidis*.

Case VI.—Mr. R., New Orleans. Typical patches on the face and arms. I was asked by Dr. Hopkins to investigate the case. A fungus was grown with the characters of *Blastomycoides tulanensis*.

Case VII.—Negro, New Orleans. Framboesiform lesions on face. I was asked by Dr. van Studdiford to investigate the case mycologically.

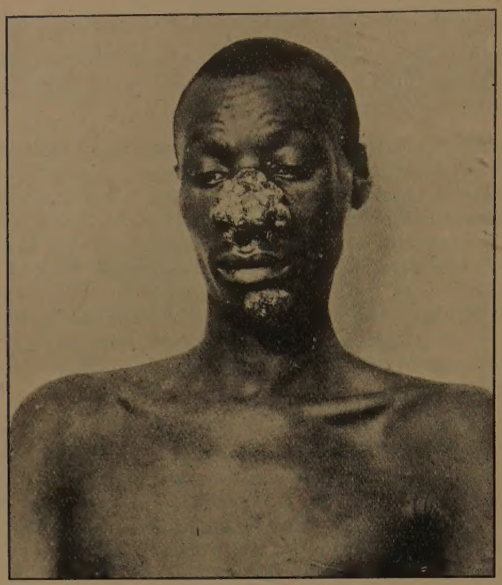

Fig. 2.—Blastomycosis (Dr. Hopkins' Case).

Case VIII.—Mrs. B., New Orleans. Large verrucoid patches on the right forearm. A fungus was isolated with the characters of *Blastomycoides tulanensis.*

Case IX.—Mr. O. P., New Orleans. Typical verrucoid patches on the face. A fungus was isolated with the characters of *Blastomycoides tulanensis.*

Ætiology of Blastomycosis Cutis Verrucosa.

General Remarks.—It is generally stated that blastomycosis cutis verrucosa is caused by *Cryptococcus dermatitidis* Gilchrist and Stokes. (Syn. *Cryptococcus gilchristi* Vuillemin). I have examined cultures isolated by me from several cases and also cultures sent from various sources, and I have come to the conclusion that the term covers several fungal species.

The fungi I have grown from various cases and the cultures I have received from various sources, labelled *Cryptococcus dermatitidis* (*Blastomyces*, or *Cryptococcus gilchristi*) may be divided into two groups :—Those of the first group produce in glucose agar a growth with a smooth, often shiny surface, and frequently gas-ferment glucose and levulose and other sugars; they have nothing to do with *Cryptococcus* or *Blastomyces dermatitidis*, as originally described by Gilchrist and Stokes ; they are fungi of the genera Monilia, Saccharomyces and Cryptococcus, *sensu stricto.* The fungi of the second group produce on glucose agar a fluffy growth, somewhat resembling the growth of certain Trichophytons, and do not gas-ferment any sugars ; these latter correspond—although only very partially—to the description of the fungus originally given by Gilchrist and Stokes: *Cryptococcus dermatitidis* (*Blastomyces dermatitidis*), but they certainly do not belong to the genus Cryptococcus, as the mycelium in glucose agar is very abundant and aerial hyphæ are numerous.

As apparently, for botanical reasons, the generic term "Blastomyces," used by Gilchrist, cannot stand for the designation of these fungi, I have suggested the

creation of a new temporary genus: *Blastomycoides*, which should be placed in the family Oosporaceæ, rather than in the family Cryptococcaceæ.

Genus Blastomycoides Castellani.—This temporary genus may be defined as follows: "Oosporaceæ, with abundant mycelium and aerial hyphæ when grown on glucose agar; abundant mycelium with, at times, lateral conidia when grown in glucose broth hanging drops; do not gas-ferment any sugar. In the lesions, spore-like bodies with well-defined double contour and well-marked granulations present without any mycelium." This genus, in all probability, contains a number of species, but for the time being the following may be differentiated:—*Blastomycoides dermatitidis*, *Blastomycoides tulanensis*, *Blastomycoides immitis*.

Blastomycoides dermatitidis Gilchrist and Stokes emen. Castellani. (Synonyms: *Blastomyces dermatitis* Gilchrist and Stokes, 1898; *Oidium dermatitis* Ricketts; *Cryptococcus gilchristi* Vuillemin; *Zymonema gilchristi* de Beurmann and Gougerot.)

In the lesions large roundish spores are found, 10 to 16 microns, with a well-marked double contour. On glucose agar the growth is white and often fluffy; abundant mycelium is present; several tufts of longer aerial hyphæ are often seen in the centre. In mannitol agar (1 per cent.) the growth is white-greyish with a peculiar woolly surface. In glycerine agar (1 per cent.) the growth is white, fluffy. On potato the growth is abundant, with abundant white duvet. In glucose broth and other sugar broths the growth takes place all over the medium, including the surface portion, and not only at the bottom of the tube. In glucose broth and peptone water hanging drops, only mycelium threads are seen, no free spores and often no lateral conidia: if these are present they are sessile. Gelatine is not liquefied. No gas fermentation of any sugar.

Blastomycoides tulanensis Castellani.—In the lesions spore-like bodies only are found, roundish or oval, 8 to 16 microns, with well-marked double contour and granules in the protoplasma, well-marked and of fairly large size. On glucose agar the growth is usually white and somewhat fluffy, this being due to tufts of aerial hyphæ.

TABLE SHOWING DIFFERENTIAL CULTURE CHARACTERS BETWEEN *Blastomycoides dermatitidis*, *Blastomycoides tulanensis*, *and Blastomycoides immitis*.

(After two weeks' incubation at 26° C.)

	Glucose broth	Mannitol agar	Glycerol agar	Potato	Hanging-drop cultures
Blastomycoides dermatitidis Gilchrist	Grows at surface and bottom	White-greyish, often woolly surface	White, fluffy	White fluffy surface	Lateral conidia supported by sterigmata usually absent
Blastomycoides tulanensis Castellani	Grows often at bottom only	White, often furrous radiating from centre	Nodular with slight white duvet	Crinkled or granular growth often brownish	Round lateral conidia supported by well-developed sterigmata often present
Blastomycoides immitis Gilchrist	Grows at the surface and bottom	Dark slate colour	White-greyish fluffy surface, with woolly appearance	White, fluffy	Lateral conidia supported by sterigmata usually absent

GENUS CRYPTOCOCCUS Kützing, 1833.—As some of the cultures which I have received for investigation, said to be isolated from cases of blastomycosis, are cultures of the genus Cryptococcus *sensu stricto* and Monilia, it may be of advantage to say a few words on these two genera.

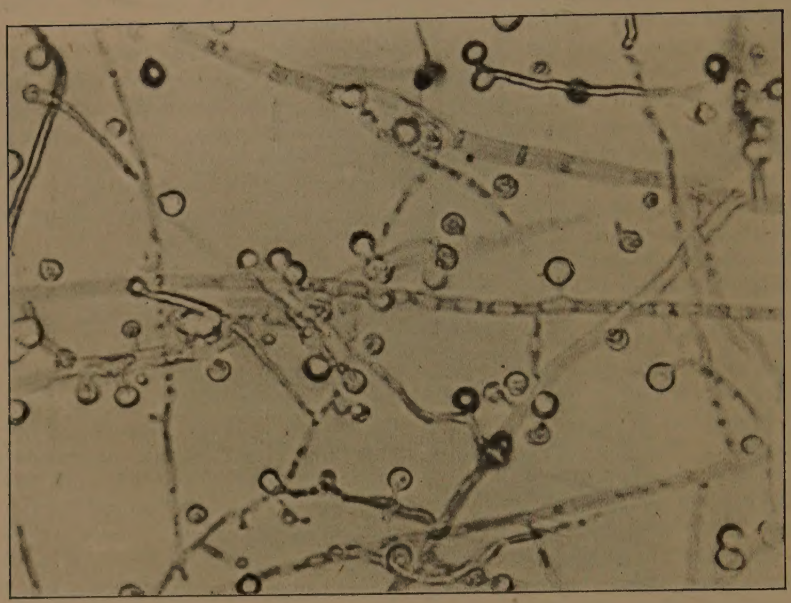

FIG. 4.—*Blastomycoides tulanensis* (hanging drop culture).

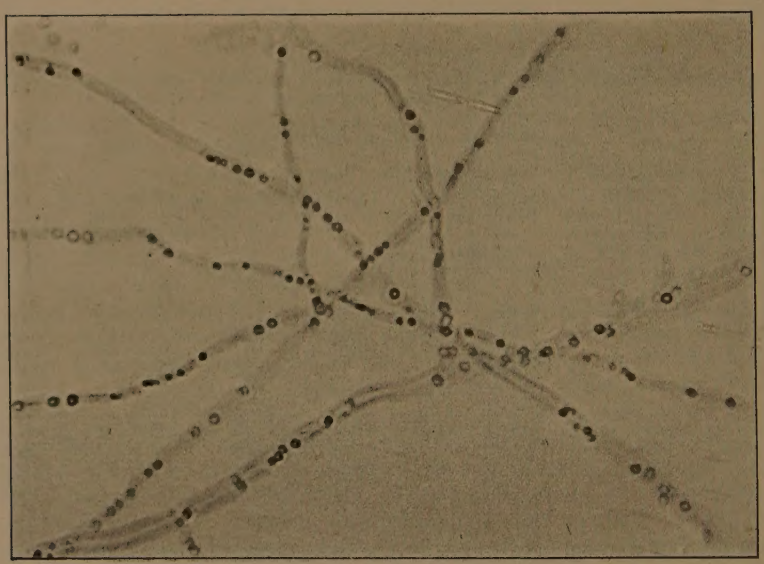

FIG. 3.—*Blastomycoides dermatitidis* (hanging drop culture).

Definition of Genus Cryptococcus.—Cryptococcaceæ with vegetative elements not elongate; pathogenic and non-pathogenic with, at times, well-developed double contour, at times the double contour is very indistinct; no globule of fat and only one bud at a time, and no formation of thick pellicle on fluid sugar media. Can be cultivated. Some species gas-ferment glucose and other sugars.

Principal Species.—For reasons already stated, and principally owing to the presence of a large amount of mycelium in cultures, the fungus described by Gilchrist—*Cryptococcus* (*Blastomyces*) *dermatitidis*—cannot be placed in this genus, as has generally been done hitherto. A fungus found by me, however, in certain cases of blastomycosis of the tongue might be placed in this genus. This fungus is *Cryptococcus macroglossiæ.*

FIG. 5.—*Cryptococcus macroglossiæ.*

Cryptococcus macroglossiæ (*Monilia macroglossiæ*).—In Ceylon, during the period 1903-1915, I observed three cases of a peculiar type of macroglossia of blastomycetic origin. Four years ago, an interesting case of macroglossia of the same type was kindly sent to me by my friend Dr. Broughton-Alcock, and in this case, too, I isolated a yeast-like organism. A full account of the case from a clinical point of view will be given at an early date by Dr. Broughton-Alcock and myself.

Description of the Organism.—Yeast-like fungus, Gram-positive, not acid-fast. The individual cells are oval, of rather large dimensions, the maximum diameter varying between 4 and 5 microns.

Cultural amd Biochemical Characters.—*Glucose agar.*—Abundant growth, smooth surface, white colour. *Ordinary agar.*—Same characters as on glucose agar, but less abundant. *Glycerine.*—Not liquefied. *Serum.*—Not liquefied. *Sugar peptone waters.*—Does not produce gas in any sugar or other carbohydrate. Very rarely it may produce a slight amount of acidity in glucose. *Litmus milk.*—No change. *Agglutination.*—Agglutinated by the patient's blood (1 in 400); not agglutinated, or only very slightly, by the blood of patients suffering from furunculosis blastomycetica.

Presence of Asci and Mycelium.—Asci have never been observed, even in very old cultures; a little mycelium is not rarely visible in certain cultures, especially in fluid media. It is therefore probably more correct to place this fungus in the genus Monilia instead of the genus Cryptococcus, as I originally did. If we place it in the genus Monilia it belongs to the *zeylanica* type (absence of gas in every sugar); it differs from *Monilia zeylanica* in not producing pigment, the cultures of *M. zeylanica* being yellow. The correct name for the organism would be *Monilia macroglossiæ* Castellani (syn.: *Cryptococcus macroglossiæ* Castellani).

Genus Monilia Persoon, 1797. — *Ætiology.* — As regards the botanical characters of the genus Monilia, the original definition by Persoon is *Stipitata aut effusa byssoidea. Fila moniliformis articulata.* These fungi are stated to be characterized by the sporophores being simple or subsimple, and producing by constriction at their extremities, a chain of large, lemon-shaped conidia, often provided with a disjunction apparatus. The general tendency at the present time, however, is to extend the term "Monilia," so as to include all those organisms of the family *Oosporaceæ* Saccardo, 1886, the vegetative body of which (thallus) in its parasitic life (*in situ* in the lesions) appears composed of mycelial threads and free budding forms, some of the mycelial filaments being long and branched, and of rather a large size, and often presenting arthrospores. In the saprophytic life (cultures on the usual solid laboratory media) mostly yeast-like, roundish or oval bodies are seen, while mycelial filaments are very scarce or absent, and when present they are rather short and consist only of a few articles. Some monilias show very little mycelium also in the lesions. Monilia fungi very often ferment glucose and other carbohydrates with the production of gas.

Classification.—Morphologically, monilias may be separated into two groups: (1) With roundish conidia, and (2) with oval or elongated conidia. Morphological characters, however, will not help further in the classification of these fungi, and for some years I have recommended a biochemical classification. For practical purposes monilias may be conveniently classified according to some of their biochemical characters, as follows:—

(1) Gas produced in glucose only: *Monilia balcanica* Castellani group.
(2) Gas produced in glucose and levulose only: *Monilia krusei* Castellani group.
(3) Gas produced in glucose, levulose, and maltose: *Monilia pinoyi* Castellani group.
(4) Gas produced in glucose, levulose, maltose, and galactose: *Monilia metalondinensis* Castellani group.
(5) Gas produced in glucose, levulose, maltose, galactose, and saccharose: *Monilia tropicalis* Castellani group.
(6) Gas produced in glucose, levulose, and saccharose; *Monilia guillermondi* Castellani group.
(7) Gas produced in glucose, levulose, galactose, saccharose, and inulin: *Monilia macedoniensis* Castellani group.
(8) Gas produced in dextrin, in addition to other sugars: *Monilia pseudolondinensis* Castellani group.
(9) Gas produced in lactose, in addition to other sugars: *Monilia pseudotropicalis* Castellani group.
(10) Absence of gas fermentation in any sugar: *Monilia zeylanica* Castellani group.

TABLE II.—Biochemical Characters of Certain Monilias.

	Glucose	Levulose	Maltose	Galactose	Saccharose	Lactose	Mannitol	Dulcitol	Dextrin	Raffinose	Arabinose	Adonitol	Inulin	Sorbitol	Starch	Glycerine	Inositol	Salicin	Amygdalin	Isodulcitol	Erythrite	Gelatine	Serum	Litmus milk		Remarks
Monilia zeylanica Castellani	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	Yellowish	
Monilia zeylanoides Castellani	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	White	Produces no discoloration of lead-agar
Monilia (cryptococcus) macroglossiæ Castellani	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	,,	Produces black discoloration of lead-agar
Monilia balcanica Castellani	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	,,	
Monilia parabalcanica Castellani	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	,,	
Monilia krusei Castellani	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	,,	
Monilia parakrusei Castellani	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	,,	
Monilia (cryptococcus) Castellanii Re	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	Yellowish or reddish-brownish	This fungus is probably a true cryptococcus. The peculiar reddish-brownish colour is best seen in old potato cultures
Monilia pinoyi Castellani	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	White	
Monilia nabarroi Castellani	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	,,	
Monilia metalondinensis Castellani	G	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	,,	
Monilia pseudolondinensis Castellani	G	G	G	G	O	O	O	O	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	,,	
Monilia alba Castellani	G	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	,,	
Monilia pseudolondinoides Castellani	G	G	G	G	O	O	O	O	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	,,	
Monilia africana Macfie, 1921	G	G	G	O	G	O	O	O	G	G	O	—	O	O	O	O	O	O	O	O	O	O	O	O	,,	
Monilia albicans Robin emen. Castellani and Chalmers	G	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	+	+	O	,,	
Monilia tropicalis Castellani	G	G	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	,,	
Monilia metatropicalis Castellani	G	G	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	,,	
Monilia rhoi Castellani	G	G	O	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	,,	
Monilia guillermondi Castellani	G	G	O	O	G	O	O	O	O	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	,,	
Monilia pseudoguillermondi Castellani	G	G	O	O	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C or P	,,	
Monilia macedoniensis Castellani	G	G	O	G	G	O	O	O	O	O	O	O	G	O	O	O	O	O	O	O	O	O	O	C	,,	
Monilia macedoniensoides Castellani	G	G	O	G	G	O	O	O	O	O	O	O	G	O	O	O	O	O	O	O	O	O	O	O	,,	
Monilia chalmersi Castellani	G	G	O	G	G	O	O	O	O	O	O	O	G	O	O	O	O	O	O	O	O	O	O	O	Dark brown	
Monilia parachalmersi Castellani	G	G	O	G	G	O	O	O	O	O	O	O	G	O	O	O	O	O	O	O	O	+	O	C	White	
Monilia bronchialis Castellani	G	G	G	O	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	,,	
Monilia pseudotropicalis I	G	G	O	G	G	G	O	O	O	O	G	O	O	O	O	O	O	O	O	O	O	O	O	C	,,	
Monilia pseudotropicalis II	G	G	O	G	G	G	O	O	O	O	O	O	G	O	O	O	O	O	O	O	O	O	O	O	,,	
Monilia pseudotropicalis III	G	G	O	G	G	G	O	O	O	O	O	O	G	O	O	O	O	O	O	O	O	O	O	C	,,	
Monilia pseudotropicalis IV	G	G	O	G	G	G	O	O	O	G	O	O	G	O	O	O	O	O	O	O	O	O	O	O	,,	

G = production of gas. C = production of clot. O = negative result—gas absent, no clotting.

It must be kept in mind that certain sugar reactions are not constant, and several species of monilia may, after a time, lose their power to ferment some carbohydrates. Hence the determination of some species can be carried out only with strains very recently isolated. It must also be kept in mind that monilias presenting the same biochemical reactions may differ enormously as regards pathogenicity. Some may produce a severe infection when inoculated into rabbits, while others may be quite harmless.

(2) *Blastomycosis Ulcerativa Profunda seu Mutilans.*

(Ophuls type, Californian type, Coccidioides type.)

(Synonyms: Blastomycosis coccidioides, Blastomycosis Wernicke-Ophuls, Blastomycosis coccidioides type.) In most cases some verrucoid lesions are present, but in addition, large, deep ulcers develop. The course is progressive, and no treatment is of any avail. When the lesions are on the feet, legs, hands and arms, amputation may be resorted to.

This type of blastomycosis has been reported from South America and from California.

Ætiology.—It is said that the fungus found in this variety differs from the fungus found in the usual verrucose type; also that in the ulcerative lesions large roundish bodies up to 80 microns are seen, with numerous spores. The fungus has been called *Coccidioides immitis.* The following is the description usually given:—

Coccidioides immitis Rixford and Gilchrist, 1896.

Synonyms: *Coccidioides pyogenes* Rixford and Gilchrist, 1896; *Oidium coccidioides* Ophuls, 1905; *Oidium protozoides* Ophuls, 1905; *Posadasia esferiformis* Canton, 1898; *Oidium immite* Verdun, 1907. Discovered by Wernicke in 1882 in America, in a patient with patches resembling a tuberculide and gummata. In the lesions roundish bodies are seen of various sizes, 3 to 80 microns in diameter, with a well-defined thick membrane. Inside some of the bodies numerous spores may be seen. This genus is not well defined.

FIG. 6.—Blastomycosis coccidioides.

Cultures.—The fungus is said to grow under two types: (*a*) a saccharomyces-like type, reproduced by budding; (*b*) a filamentous type. The colonies have been described as being roundish, slightly elevated, but deepening into the medium, grey or white, but when old often become brownish. In old cultures, chlamydospores may be present. The biochemical properties of the fungus are not known.

Remarks.—I have investigated two cultures sent to me labelled "*Coccidioides immitis.*" Culturally, on glucose agar they are very similar to *Blastomycoides dermatitis* of Gilchrist, *sensu stricto*, although the cultures often show a light fawn colour, usually lacking in glucose agar cultures of *Blastomycoides dermatitidis*, they have also the same characteristic of growing all over in broth tubes, and not only at the bottom. If mannitol and glycerine media are used the fungus grows differently from *Blastomycoides dermatitidis.*

The following is a description of *Blastomycoides immitis* based on the characters of the two strains of the fungus in my possession:—

Blastomycoides immitis, Rixford and Gilchrist, 1896, Em. Cast.

The fungus culturally when grown on glucose agar is similar to *Blastomycoides dermatitidis*; on glucose agar the growth is a white or light fawn colour and somewhat fluffy owing to tufts of aerial hyphæ. In mannitol agar (1 per cent.) after two weeks the growth becomes a peculiar slate-black colour: in glycerine-agar it has a greyish woolly surface. In the hanging-drop cultures (glucose-broth, glucose peptone water, simple peptone water) mycelium only is found with no free budding cells, and usually no lateral conidia. In glucose broth and other sugar broths the growth takes place in every portion of the medium, including the surface.

The lesions caused in man by this fungus are clinically somewhat different frem those caused by *Blastomycoides dermatitidis*, and therefore in my opinion it is justifiable even apart from cultural difference, to consider it a separate species.

(3) *Blastomycosis Purulenta Profunda.*

(Blastomycosis, Busse type; Blastomycosis subcutanea purulenta.)

This type of blastomycosis is considered a variety of blastomycosis cutis for convenience sake. It is characterized by the presence of subcutaneous and deep abscesses, and purulent conditions of the bones, periosteum, and internal organs. The skin proper is not affected, and verrucoid patches are never present.

Ætiology.—The condition is caused by *Cryptococcus hominis* Vuillemin, 1901, a term which probably covers several varieties or even species.

Cryptococcus hominis Vuillemin, 1901. (Synonyms: *Saccharomyces* (sp. ?) Busse, 1894; *Atelosaccharomyces bussebuschki* de Beurmann and Gougerot, 1909; *Atelosaccharomyces rudeli* de Beurmann and Gougerot, 1911.)

Found by Busse in abscesses in a woman. In the pus the fungus presented itself in the shape of oval bodies, with a membrane having a double contour. These elements were arranged in groups, each group embedded in an amorphous substance and surrounded by a capsule. Culturally the fungus showed only roundish budding forms, no mycelium, no asci. Growth on solid media generally white. Gelatine not liquefied. Glucose fermented. Pathogenic to rabbits, white mice and dogs.

(4) *Blastomycosis Glutealis.*

This condition was described by Kartulis some years ago in Egypt. I have often observed it in Ceylon. The skin of the gluteal region—one nate or both nates—presents a diffuse induration, and is cribrated with the opening of sinuses, from which a thin pus exudes. The sinuses may be very deep and connected with each other, but in cases I have seen did not connect with the intestine. The pus does not

contain grains, as is the case with actinomycosis. The patient may complain of pain and discomfort on sitting down. The disease is chronic.

Ætiology.—The mycological investigation of the condition cannot be considered completed. The fungi found seem to belong to the genus Monilia and the genus Cryptococcus.

(5) *Furunculosis Blastomycetica Cryptococcica.*

(Folliculitis decalvans cryptococcica, *pro parte.*)

(Synonyms : furunculosis cryptococcica ; pseudofurunculosis blastomycetica ; furunculosis moniliaca; furunculosis mycetica ; folliculitis decalvans saccharomycetica ; folliculitis decalvans moniliaca.)

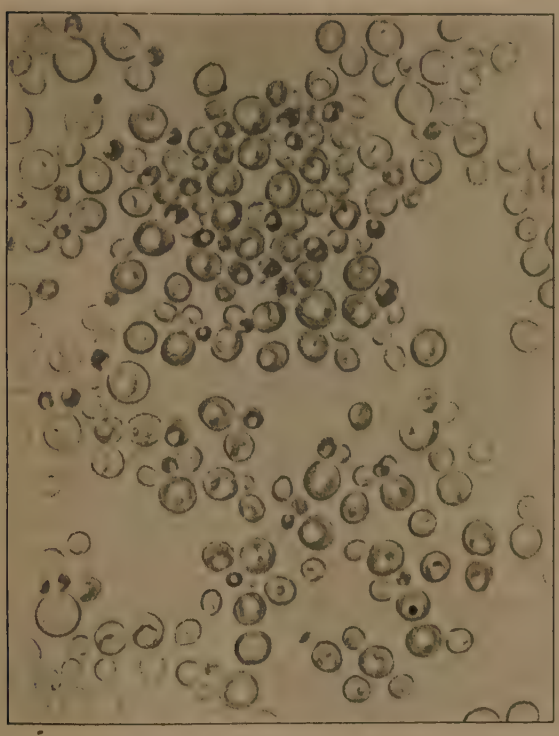

FIG. 7.—*Cryptococcus castellanii*, Re.

FIG. 8.—*Cryptococcus castellanii*, Re. Glucose agar culture.

History.—Some years ago I described a peculiar type of blastomycosis indistinguishable clinically from ordinary furunculosis, which I called at the time "furunculosis cryptococcica," and as the condition in the first two cases affected principally the scalp under the form of a purulent folliculitis and loss of hair, I also suggested for it the term "folliculitis decalvans cryptococcica." To date I have seen five cases : three patients contracted the infection in Great Britain, and two in India.

Ætiology.—The fungi found are yeast-like, and it is difficult to decide whether they belong to the genus Cryptococcus or to the genus Monilia. One of them (*Cryptococcus*

castellanii Re) was fairly completely described by me, and later by Dr. Re, who named it *Cryptococcus castellanii*. The strains of fungus isolated from the Indian cases are somewhat different from the organisms grown from the English cases, and differ also, though slightly, among themselves.

Cryptococcus castellanii Re.—Description of the organism: Morphologically a yeast-like organism, Gram-positive, not acid-fast. The individual cells are somewhat rounded or oval. Maximum diameter of most cells 3 to 4 microns. The fungus is seldom detected microscopically in the pus of the boil-like lesions, staphylococci being generally present in very large numbers; cultural methods are necessary; the cultures from the pus, as a rule, look like cultures of *Staphylococcus aureus*. It may be necessary to make a dozen or more preparations from what looks a pure staphylococcus growth to find a few yeast-like cells. By plating and re-plating on glucose agar media the fungus is finally isolated.

Cultural and Biochemical Characters.—The fungus grows abundantly on *glucose agar* and also grows well, though less abundantly, on ordinary agar. The cultures on glucose agar are at first white, but after a few days show a characteristic yellowish or yellowish-brownish pigmentation. Gelatine and serum are not liquefied.

Lead agar is not darkened during the first two weeks; later, a slight darkening may take place.

Sugar Peptone Waters.—The fungus when recently isolated has very little or no fermentative action on any sugar; it may produce a slight acidity in glucose and levulose, very seldom a slight amount of gas. When the fungus has been transplanted several times its fermentative action is greatly increased and it generally produces acid and gas in glucose and levulose, and occasionally slight acidity in galactose; it does not form gas in any other sugars (see Table).

Litmus Milk.—The medium is not clotted, a slight acidity may be present.

Agglutination.—The fungus is agglutinated by the patient's blood in certain cases, up to 1 in 400.

Ascospores, Mycelium.—I have never observed asci even in very old cultures; mycelium in small amount is not rarely present in certain media, especially fluid media.

Symptomatology.—The clinical picture of this blastomycosis is totally different from the usual types of blastomycosis cutis, which are characterized by the presence of patches with vegetating capillary excrescences which give them a characteristic verrucose or warty appearance.

Furunculosis blastomycetica is clinically indistinguishable from ordinary severe furunculosis. Boils, indistinguishable from ordinary boils, may be present on the face and body, but the region mostly affected, as a rule, is the scalp. In this region numerous pustules, flattened or conical, each pierced by a hair, may be seen; in addition, there may be infiltrated lesions which somewhat resemble flat carbuncles, and later open and discharge through several openings.

The hair in the infected areas falls off, and patches of baldness, sometimes permanent, remain.

Illustrative Case.

Mr. D., married, aged 34, a Dane who had resided in London for twelve years preceding admission; he was fond of all outdoor sport, and was a famous football player. The condition started in March, 1921, with apparently follicular pustules on the scalp, and two or three furuncular-like lesions on the forehead and face. Later, extremely painful carbuncle-like lesions developed. A bacteriologic examination of the pus was made at a well-known clinical laboratory in London, and *Staphylococcus aureus* was found. An autogenous staphylococcus vaccine and also a stock vaccine were given for eighteen months without any benefit. On the advice of his medical attendant the patient then came to consult me.

Apart from the boil on the left forearm and one on the supra-orbital region, all the lesions were on the scalp ; several patches of baldness, with the skin smooth and whitish, were plainly visible ; there were also numerous follicular pustules, some flat, some conical, and most of them surrounded by a zone of hyperæmia. Two extremely painful carbuncle-like lesions, one not yet opened and the other with several openings discharging, were present. I made a bacteriologic and a mycologic examination. Microscopically, the pus contained only Gram-positive cocci. The dextrose-agar tubes inoculated with the pus showed abundant growth of *Staphylococcus aureus*. The microscopic examination of the growth, however, showed here and there a yeast-like cell in several tubes. After plating and replating, this yeast-like organism was isolated with great difficulty. Later, I grew the same fungus from a number of lesions, some of which were unopened.

FIG. 9.—Furunculosis blastomycetica.

It was a cryptococcus with the following principal characters: Cultures on dextrose-agar were abundant with a smooth surface, at first white and later yellowish. The fungus did not produce gas in any carbohydrate at first; later, it caused production of gas in dextrose and levulose. It was agglutinated by the patient's blood in high dilution (1 in 400). An interesting point arises: Which organism was the true causative agent of the condition, the cryptococcus or the staphylococcus? In my opinion, it was the cryptococcus, for the following reasons : Staphylococcus vaccines did not have any beneficial action whatever. The cryptococcus was agglutinated by the patient's blood, and the condition improved and finally disappeared under a treatment consisting of massive doses of potassium iodide given internally, and a cryptococcus vaccine subcutaneously injected. It is well known that potassium iodide does not have any beneficial action on *Staphylococcus furunculosis*, it makes it much worse.

Diagnosis.—The diagnosis can be made only by mycologic method. In all cases of persistent furunculosis that do not answer to staphylococcus vaccine, the possibility of furunculosis blastomycetica should be kept in mind.

Prognosis.—The disease does not have a tendency to spontaneous cure.

Treatment.—Potassium iodide in large doses, given for long periods, often induces a cure. A vaccine prepared with the fungus seems to be useful, but used alone is not sufficient to bring about a cure.

ADDENDUM.

Superficial Infections due to Yeast-like Fungi.

"Blastomycosis cutis" covers all the forms of blastomycosis in which well marked lesions in the skin, either verrucoid or gummatous or furunculoid, are present; there are, however, a number of very superficial affections of the skin, caused by yeast-like organisms, for which some years ago I proposed the term "blastomycosis epidermica."

(6) *Blastomycosis (Cryptococcosis) Epidermica.*

Remarks.—Blastomycosis epidermica was described by me in Ceylon some years ago. Clinically, it has nothing to do with the usual types of blastomycosis, but it may be called blastomycosis, as it is caused by a yeast-like organism.

Synonyms.—Saccharomyces epidermica, Cryptococcosis epidermica.

History and Geographical Distribution.—While in Ceylon, I noticed on the skin of one of my bungalow servants several brownish, dirty-looking patches, which looked very much like dirt. He told me, however, that they did not disappear when soap was used. I made scrapings and saw that these patches consisted of a large number of budding cells which I believed to be saccharomyces. I found the same patches not only in other natives but also in Europeans, especially on the chest and arms, and I called the condition "saccharomycosis epidermica." I did not succeed in growing the fungus. Chalmers and others confirmed my observations in the Sudan and North Africa, but the organism has not yet been cultivated.

Ætiology.—The causal organism is *Cryptococcus epidermidis* Castellani, 1914.

Symptomatology.—The condition is fairly frequent in natives and Europeans who have resided for some years in the tropics. It is characterized by the presence on the arms, and more rarely on the chest and neck, of small, roundish, dirty, yellow or brownish patches, which can generally be removed by thorough scraping. These patches consist of large numbers of blastomyces-like elements of various sizes, rounded or oval, which, so far, have not been cultivated.

Treatment.—Ordinary soap does not remove the patches, but thorough scraping with sand soap and hot water is generally sufficient to remove them. In obstinate cases a salicylic sulphur ointment is useful.

Clinical Variety of Blastomycosis Epidermica.—Blastomycosis (cryptococcosis) epidermica, alba and rosea: white patches, consisting solely of yeast-like fungi, without inflammatory signs, are occasionally seen, especially in natives. I have grown the fungi several times; they belong to the genera Cryptococcus, Saccharomyces and Monilia. In a case with pinkish patches, a cryptococcus was present which when cultivated on laboratory media gave rise to pink colonies.

Intertrigo Blastomycetica and Dermatitis Blastomycetica Interdigitalis.

(*Synonyms.*—Intertrigo saccharomycetica, intertrigo cryptococcica, intertrigo moniliaca.)

Intertrigo blastomycetica was first described by me in Ceylon in 1907. In Europeans, the affected skin—usually the skin of the inguinal region—is reddened, and there may be a slight exudation. The border of the eruption may be fairly well marked, but it is not distinctly raised. In many cases there is not much itching. In 1907, in scrapings, I found a yeast-like fungus which I called *Saccharomyces samboni*. In other cases I found organisms of the genera Monilia and Cryptococcus. In recent years a similar condition, saccharomycosis or blastomycosis interdigitalis, has been described by several observers, and I have seen some cases myself and Pollaci has called one of the cryptococcus-like fungi found in it *C. interdigitalis*.

Dermatitis interdigitalis blastomycetica and Epidermophytica (mixed infection).

In the majority of my cases an epidermophyton was present in addition to numerous yeast-like bodies, that is, in superficial scrapings only yeast-like organisms were present, while in deep scrapings the yeast-like fungus disappeared or was extremely scanty and an epidermophyton was present.

John Bale, Sons & Danielsson, Ltd. 83-91, Great Titchfield Street, London, W. 1.